Endokrynologia Polska
DOI: 10.5603/EP2013.0031
Tom/Volume 64; Numer/Number 6/2013
ISSN 0423–104X

Pancreatic neuroendocrine neoplasms — management guidelines (recommended by the Polish Network of Neuroendocrine Tumours)

Nowotwory neuroendokrynne trzustki — zasady postępowania (rekomendowane przez Polską Sieć Guzów Neuroendokrynnych)

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Abstract
We present revised diagnostic and therapeutic guidelines for the management of pancreatic neuroendocrine neoplasms (PNENs) proposed by the Polish Network of Neuroendocrine Tumours.
These guidelines refer to biochemical (determination of specific and nonspecific neuroendocrine markers) and imaging diagnostics (EUS, CT, MR, and radioisotope examination with a ^{68}Ga or ^{99}Tc labelled somatostatin analogue).
A histopathological diagnostic, which determines the further management of patients with PNENs, must be necessarily confirmed by immunohistochemical tests. PNENs therapy requires collaboration between a multidisciplinary team of specialists experienced in the management of these neoplasms. Surgery is the basic form of treatment. Medical therapy requires a multidirectional procedure, and therefore the rules of biotherapy, peptide receptor radionuclide therapy, chemotherapy and molecular targeted therapy are discussed. **(Endokrynol Pol 2013; 64 (6): 459–479)**

Key words: *pancreatic neuroendocrine neoplasms; functioning; non-functioning; diagnosis; therapy; guidelines*

Streszczenie
W niniejszej publikacji przedstawiono zaktualizowane zalecenia dotyczące diagnostyczno-terapeutycznego postępowania w nowotworach neuroendokrynnych trzustki (PNEN) zaproponowane przez Polską Sieć Guzów Neuroendokrynnych.
Dotyczą one diagnostyki biochemicznej (oznaczanie specyficznych i niespecyficznych markerów neuroendokrynnych) i lokalizacyjnej (z uwzględnieniem EUS, CT, MR, scyntygrafii receptorów somatostatynowych z użyciem analogów znakowanych ^{68}Ga lub ^{99}Tc).
Duże znaczenie ma rozpoznanie histopatologiczne, które determinuje dalsze postępowanie z chorymi na PNEN i musi być potwierdzone badaniem immunohistochemicznym.
Terapia PNEN wymaga współpracy wielodyscyplinarnej grupy doświadczonych specjalistów zajmujących się nowotworami neuroendokrynnymi. Leczenie chirurgiczne jest postawową metodą postępowania. Dalsza terapia wymaga wielokierunkowego działania, dlatego omówiono zasady bioterapii, leczenia izotopowego, chemioterapii oraz celowanego leczenia molekularnego. **(Endokrynol Pol 2013; 64 (6): 459–479)**

Słowa kluczowe: *nowotwory neuroendokrynne trzustki; czynne hormonalnie; nieczynne hormonalnie; diagnostyka; terapia; zalecenia*

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1. Epidemiology, prognosis/survival

1.1. Pancreatic neuroendocrine neoplasms (excluding gastrinomas)

The incidence of pancreatic neuroendocrine neoplasms (PNENs) is approximately 0.32/100,000/year. PNENs account for approximately 30% of all gastroentreopancreatic neoplasms (GEP NENs). 45–60% of PNENs (in some registers up to 90%) are **non-functioning**. Despite the lack of symptoms of hormonal hypersecretion, they demonstrate the ability to produce certain substances, e.g. pancreatic polypeptide, chromogranin A, neuron-specific enolase, β-hCG subunit, calcitonin, neurotensin and other peptides. On the other hand, 40–55% of PNENs demonstrate excessive hormonal activity (**functioning tumours**), which is reflected in corresponding clinical symptoms [1–3].

Functioning PNENs include [1, 4]:
— insulinoma — secreting insulin,
— gastrinoma — secreting gastrin,
— glucagonoma — secreting glucagon,
— VIPoma — secreting vasoactive intestinal peptide,
— PPoma — secreting pancreatic polypeptide (often classified as a non-functioning tumour),
— somatostatinoma — secreting somatostatin.

Very rare functioning PNENs include: CRHoma — secreting CRH — hormone stimulating production of corticotrophin, calcitoninoma — secreting calcitonin and PNENs producing corticotrophin (ACTH), growth-hormone-releasing hormone (GHRH), neurotensin, parathyroid hormone-related peptide (PTHrP), rennin, luteinising hormone (LH) and others.

The most common functioning PNENs are insulinoma and gastrinoma [1, 4] (discussed in detail in the section on gastroduodenal neuroendocrine neoplasms (NENs).

1.2. Clinical characteristics of PNEN

Insulinoma — insulin-secreting pancreatic neoplasm is the most common functioning neuroendocrine tumour of this organ. In approximately 1% of patients, an extrapancreatic location is possible (duodenum, stomach, bile ducts, lungs) [5]. Its incidence rate is estimated at 1–3 cases/1,000,000/year. The highest incidence is observed in the fifth decade of life (between the ages of 40–45), and slightly more often in females (60%). Less than 10% of all tumours are malignant [4]. *Insulinoma* is usually single, and only 10% of patients have multiple tumours (often in multiple endocrine neoplasia type 1 [MEN1]). In approximately 4–5% they are associated with MEN1 syndrome [4, 5, 7, 8]. **Clinical symptoms** are due to hypoglycaemia, not the presence of tumour (usually it is no more than 2 cm in diameter). They result from neuroglycopenia: pains and vertigo, blurred vision, double vision, abnormal behaviour, confusion, concentration disorders, retrograde amnesia, drowsiness, hallucinations, delusions and convulsions. In approximately 12% of patients, loss of consciousness occurs with a *grand mal* seizure. Severe hypoglycaemia may result in death. Decreased blood glucose level also causes increased secretion of catecholic amines, and therefore: paleness, increased perspiration, hand tremor, nausea, palpitations, hunger (often increased body weight) and weakness. Although the hypoglycaemic episodes usually occur several hours after a meal, often in the morning, irregularly and with different duration, in approximately 6% of patients hypoglycaemia can only occur soon after a meal [9]. They may be triggered by physical effort, consumption of ethyl alcohol or a low-calorie diet [4, 6, 7, 10–12].

A positive Whipple's triad is helpful in diagnosing insulinoma:
1. Clinical symptoms suggestive of hypoglycaemia;
2. Decreased blood glucose level (< 40 mg/dL; 2.2mmol/L) measured at the time of the symptoms;
3. Relief of symptoms after intake of carbohydrates.

Prognosis: in benign tumours — very good; in over 95% of such patients, a surgical procedure results in complete recovery. In patients with distant metastases, mean survival is less than two years. Tumour diameter > 2 cm, Ki-67 > 2%, and various molecular and chromosomal disorders, e.g. loss of 3p or 6q, are factors associated with decreased survival [6–8, 10–13].

Other tumours are classified as ***rare functioning pancreatic neuroendocrine neoplasms*** (RF-PNENs). They may occur in the pancreas and in other locations. The clinical symptoms associated with the presence of such neoplasms reflect the action of a hormone secreted by the tumour. In the case of very rare neoplasms, interpretation of the symptoms is often ambiguous [4, 6].

RF-PNENs constitute < 10% of PNENs. In a large number (40–90%) of patients with RF-PNENs, hepatic metastases are present already at diagnosis [4, 6, 14].

VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA syndrome): incidence rate 0.05–0.2/1,000,000/year, malignant neoplasms in 40–70%, in ca. 3–6% associated with MEN1; location: primarily body of the pancreas (90%), also sympathetic nervous system, liver, adrenal glands. Symptoms: diarrhoea (90–100%), hypokalaemia (80–100%), dehydration (83%), acidosis, rarely skin reddening, hypercalcaemia, glucose intolerance and functioning gall bladder disorders [4, 15–18].

Glucagonoma: incidence rate 0.01–0.1/1,000,000/ /year, malignant neoplasms 50–80%; in 1–20% associated with MEN1; location: body of the pancreas; symptoms: necrolytic erythema (67–90%), glucose intolerance (38–87%), weight loss (66–96%), stomatitis, diarrhoea and hypoaminoacidemia [4, 15–18].

Somatostatinoma: very low incidence rate, malignant neoplasms > 70%, in 45% associated with MEN1,

location: pancreas (55%), duodenum/small intestine 44%, symptoms: cholelithiasis (65–90%), diabetes (63–90%), diarrhoea (35–90%) and weight loss [4, 15–18].

GHRHoma: unknown incidence rate, malignant neoplasms > 60%, location: pancreas (30%), lungs (54%), small intestine (7%), other (9%), associated with MEN1 in 16%, symptoms: acromegaly [4, 15, 16].

ACTHoma: low incidence, malignant neoplasms > 95%, pancreatic location (4–16%), others — extrapancreatic location, rarely associated with MEN1, symptoms: Cushing's syndrome [4, 15, 16].

PNEN causing carcinoid syndrome: secretes serotonin or tachykinins, very rare: pancreatic location < 1%, malignant neoplasms 60–88%, rarely associated with MEN1, symptoms: carcinoid syndrome [4, 15, 16].

PTHrPoma: very rarely located in the pancreas, malignant neoplasms 84%, rarely associated with MEN1, symptoms: hypercalcaemic syndrome or, in the case of hepatic metastases — abdominal pain [4, 15, 16].

Prognosis: in RF-PNENs, it depends on the size of the tumour and the presence of distant metastases. The five-year survival rate in the case of advanced disease is estimated at 29–45%. Ki-67 > 2%, distant metastases, chromosomal disorders and presence of cytokeratin-19 are unfavourable prognostics [4, 6, 13, 15, 16, 19].

Non-functioning pancreatic neuroendocrine neoplasms (NF-PNENs) do not cause characteristic symptoms of hormonal hypersecretion. In some tumours, immunohistochemical methods have revealed the presence of various hormonal substances produced by these neoplasms, but not secreted into the blood circulation (or secreted in quantities which do not result in clinical symptoms). Most of them are well-differentiated tumours. Their incidence rate is 1.8/1,000,000/year in females and 2.6/1,000,000/year in males. The frequency of detection increases with age, with the peak incidence in the 6th and 7th decades of life. In 3-53% (mean 19%), they are associated with MEN1 syndrome (the frequency is age-related, being higher in elderly patients) and in 13-17% with von Hippel-Lindau (VHL) syndrom [2, 20–23].

Symptoms: NF-PNENs are usually diagnosed late, when they are of large size, cause pressure on the adjacent organs or invade them, or produce distant metastases [2, 3]. The most common symptoms include: abdominal pain (35–78%), weight loss (20–35%), loss of appetite and vomiting (45%). Less common are internal haemorrhages (4–20%), jaundice (17–50%) or palpable tumours in the abdomen (7–40%) [2, 24–26]. Recent studies by Italian researchers have demonstrated that hepatic metastases are observed in 32% of patients with a newly diagnosed NF-PNEN [27]. This value is significantly lower compared to previous studies (46–73%) [21, 28–30].

Prognosis: The mean survival of patients with NF-PNENs in currently available studies is 38 months, with five-year survival of 43% [2, 21]. The mean survival of patients with distant metastases was approximately 23 months, compared to 70 and 124 months' survival in the case of a localised disease [2, 21, 31]. The histological grading of the tumour is also an important factor affecting the length of survival [2, 32]. Other unfavourable prognostic factors include: age >40 years, dynamic development of hepatic metastases (increase of 25% of their volume in 6-12 months), and occurrence of osseous metastases [2, 33, 34].

2. Diagnostics

2.1. Biochemical diagnostics

Biochemical diagnostics of hormones and markers secreted by neuroendocrine neoplasms (NENs) may be helpful in three aspects: initial diagnosis of the disease, assessment of treatment efficacy, and prognosis.

2.1.1. Non-functioning pancreatic neuroendocrine neoplasms (NF-PNENs)

Biochemical tests of PNENs can use **chromogranin A** (CgA), which is a marker of most NENs. On the other hand, the level of chromogranin B (CgB) may be elevated when the level of CgA is within the reference range [2, 35, 36].

NF-PNENs often secrete **pancreatic polypeptide** (PP). A simultaneous measurement of CgA and PP concentration increases the diagnostic sensitivity of PNENs from 74% to 90%. PP is secreted in large quantities by a significant group of NENs of the entire gastrointestinal tract (50–80% of PNENs).

The following indicators are sometimes used in biochemical diagnostics of non-functioning NENs: **neuron specific enolase** (NSE) and the β subunit of **human chorionic gonadotropin** (hCG). NSE is mainly determined in neuroendocrine carcinoma (NEC), if the CgA concentration is normal.

The concentration of certain peptides, mostly insulin, gastrin and PP, increases significantly after meals; it may remain elevated for more than six hours after a meal [4]. Therefore, blood for the assay should be collected only after overnight fasting. For some markers, e.g. CgA, it is not necessary to collect blood under fasted conditions. If blood samples are not collected under fasted conditions, this fact should always be mentioned to ensure the proper interpretation by the laboratory. Moreover, the blood concentrations of all NEN markers, except insulin, are elevated in patients with renal failure, so it is difficult to interpret results in such patients. Among numerous markers assessed in the blood, CgA is a prognostic factor for most NENs [37, 38, 39].

2.1.2. Functioning pancreatic neuroendocrine neoplasms (F-PNENs)

Biochemical diagnostics of all F-PNENs requires the evidence of increased serum concentrations of specific hormonal markers (e.g. gastrin in Zollinger-Ellison syndrome (ZES) or insulin in insulinoma) in combination with clinical symptoms/Laboratory changes indicating the hypersecretion of an appropriate hormone, such as excessive secretion of gastric juice in ZES, hypoglycaemia in insulinoma, etc. [4]. In a great number of sporadic NENs, the type of cells may change and tumours may produce various additional peptides (apart from those specific for the tumour). It is related to worsening of the prognosis, especially when the tumour additionally secretes ACTH [40, 41].

Most insulinomas are 'benign' tumours with proper serum CgA levels which increase with metastases.

Insulinoma

The diagnosis of insulinoma is based on the following criteria:

— documented glycaemia ≤ 2.2 mmol/L (≤ 40 mg/dL) and concomitant inadequate concentration of insulin ≥ 6 mU/L (≥ 36 pmol/L);
— C-peptide level ≥ 200 pmol/L;
— proinsulin level ≥ 5 pmol/L.

Interpretation of the above criteria should include drug-induced hypoglycaemia by verifying the serum and/or urinary levels of sulphonylurea and its metabolites [4].

When diagnosing ***insulinoma,*** the 72-hour fasting test is still the gold standard, although some studies report that a 48-hour test may be sufficient. The fasting test is performed in inpatient conditions, with serial measurements of the blood glucose level. Patients with insulinoma usually develop hypoglycaemia within 24 hours. Increased levels of ketones in urine indicate the proper fasting test in healthy people. In 5% of patients, hypoglycaemia may occur after meals [42]. When the symptoms of hypoglycaemia occur and the glucose level in the blood is ≤ 2.2 mmol/L (≤ 40 mg/dL), the blood should be collected for C-peptide, proinsulin and insulin assays. The lack of adequate suppression of insulin in hypoglycaemia confirms the presence of an independently secreting insulinoma-type tumour [4].

In one of the recent studies, the most sensitive criterion for diagnosing insulinoma was the coexistence of elevated proinsulin levels and fasting glycaemia of ≤ 2.5 mmol/L (≤ 45 mg/dL) [4].

Gastrinoma

The biochemical diagnostics of gastrinoma are discussed in the section on gastroduodenal NENs (*pp. 444–458*).

2.1.3. Rare functioning pancreatic neuroendocrine neoplasms (RF-PNENs)

Biochemical diagnostics of a RF-PNEN includes confirmation of increased serum concentrations of specific biochemical markers, e.g. glucagon is suspected glucagonoma (positive result > 1,000 pg/mL), vasoactive intestinal peptide (positive result > 170 pg/mL), somatostatin (positive result in pancreatic neoplasms location is over 50 times higher than the reference values) [34].

CgA, which is a general marker, can only be used to confirm the presence of a neuroendocrine neoplasm and monitor the course of the disease, but it cannot constitute the basis for the diagnosis of functioning PNENs.

All biochemical tests should be performed during the first visit. Suspected Cushing's syndrome due to PNEN should be confirmed by 24-hour urine or midnight serum cortisol measurements, or by determination of cortisol concentration in saliva. If necessary, the determination of cortisol with the use of the dexamethasone suppression test should be performed.

The assessment of markers specific for NEN is useful in the diagnosis and monitoring of various neoplasms [43], as set out in Table I. Indications for their determination depend on the clinical presentation of the patient with a PNEN.

2.1.4. Pancreatic neuroendocrine carcinoma (PNEC)

An assessment of the CgA levels and other hormonal markers in this group of PNEC usually produces negative results. NSE may be used as a marker for these neoplasms [34].

Minimal consensus on biochemical tests:

Determination of plasma CgA level should be the basic biochemical test in patients with suspected PNENs [44]. In non-functioning NENs, pancreatic polypeptide (PP) can be used for early detection of PNENs in MEN1 and PNEC (especially with low CgA level).

*Determination of specific markers (gastrin, insulin, serotonin, VIP, glucagon, etc.) should be performed if the patient presents symptoms suggestive of a hormonal clinical syndrome. Specific dynamic tests are very rarely performed. (*evidence level 3).*

2.2. Pathomorphological diagnostics

2.2.1. Pathogenesis

The term 'pancreatic neuroendocrine neoplasms' refers to tumours arising from a pluripotent stem cell of the pancreatic ducts with neuroendocrine differentiation. The term 'islet cell tumour', frequently used in the

** evidence level according to CEBM [152]*

Table I. *Specific markers for various PNENs (modified according to [34, 43])*
Tabela I. *Specyficzne markery dla różnych PNEN (zmodyfikowane wg [34, 43])*

Tumour type	Laboratory tests	Expected results
All pancreatic NENs	CgA	Increased concentration only in metastatic tumours
Non-functioning NENs	PP, NSE, hCG	Increased concentration
Insulinoma	CgA, insulin, glucose,	Inadequate increase in the insulin/glucose concentration ratio
	C-peptide or proinsulin	Increased concentration
Gastrinoma	Gastrin	Increased concentration
Glucagonoma	Glucagon, enteroglucagon	Increased concentration
VIPoma	VIP	Increased concentration
Somatostatinoma	SST	Increased concentration
PPoma	PP	Increased concentration
MEN1	CgA, gastrin, calcium, PTH, insulin, glucagon, PP, PRL	Increased concentration of selected markers

CgA — chromogranin A; CgB — chromogranin B; hCG — human chorionic gonadotropin; 5-HIAA — 5-hydroxyindoleacetic acid; NSE — neuron specific enolase; PP — pancreatic polypeptide; PTH — parathyroid hormone; SST — somatostatin; VIPoma — tumour secreting vasoactive intestinal peptide; PRL — prolactin

Table II. *ENETS and TNM UICC/AJCC classification, 2011*
Tabela II. *Klasyfikacja TNM ENETS i AJCC/UICC, 2011*

Feature T according to TNM	TNM ENETS	TNM AJCC/UICC, 2011
T1	Tumour limited to the pancreas, < 2 cm in diameter	Tumour limited to the pancreas, < 2 cm in diameter
T2	Tumour limited to the pancreas, 2–4 cm in diameter	Tumour limited to the pancreas, > 2 cm in diameter
T3	Tumour limited to the pancreas, > 4 cm in diameter or invading duodenum or bile tract	Tumour invading the adjacent tissues, without invasion of the main vascular trunks (coeliac axis, superior mesenteric artery)
T4	Invasion of the adjacent organs or the wall of large vessels	Invasion of the wall of large vessels

past, is incorrect due to NEN histogenesis, as these neoplasms do not arise from pancreatic islets. Pathomorphological diagnostics of NENs is based on the standardised WHO classification. The diagnosis is confirmed by immunohistochemical methods, in order to assess the expression of neuroendocrine markers: chromogranin A and synaptophysin, and the Ki-67/MIB1 proliferation index. Immunohistochemical examination of the hormonal substances produced by pancreatic cells is not sufficient for the diagnosis of functioning or non-functioning tumours [34]. Pancreatic cells may demonstrate immunohistochemical expression of the analysed products even in minimal quantities, without any clinical significance.

2.2.2. Diagnostic algorithm

Histopathological diagnostics of PNENs requires an assessment of [45–50]:

— histological type according to the WHO 2010 classification;
— histological grade according to the ENETS/WHO 2010 classification;
— pTNM stage of clinical and pathological advancement (according to ENETS, AJCC/UICC of 2010) (Table II);
— each diagnosis of NEN must be confirmed by immunohistochemical examinations with the use of antibodies against chromogranin A and synaptophysin, and by the Ki-67/MIB1 proliferative activity assessment;
— in certain cases, products secreted by NENs, such as gastrin, insulin or glucagon may be assessed. These markers are more useful for detection of the metastases of functioning tumours, especially if the original site is unknown. Clinical staging of NENs is presented in Table III.

Classification of NENs according to WHO 2010 and the histological grade of NETs according to the standardised ENETS/WHO 2010 system are presented in the section on general recommendations for the management of GEP NENs (*pp. 418–443*).

Table III. *Clinical staging of PNENs*
Tabela III. *Stopień klinicznego zaawansowania PNEN*

Clinical stage	Comments
Stage IA	T1 N0 M0
Stage IB	T2 N0 M0
Stage IIA	T3 N0 M0
Stage IIB	T1-3 N1 M0
Stage III	T4, any N M0
Stage IV	Any T, any N M1

2.2.3. Prognostic factors in the histopathological report
In the histopathological examination, it should be noted that nodules smaller than 5 mm are referred to as *microadenoma*, and are not considered in the histopathological report. Multiple foci are characteristic for PNENs, especially in MEN1, in over 30% of gastrinoma cases and 13% of insulinoma cases. Therefore, a very careful microscopic assessment of the surgical material, involving cross-sections of the pancreatic parenchyma at 3 to 5 mm intervals, is necessary. In each case, an assessment of resectability is an important prognostic parameter. In order to perform it, it is necessary to evaluate macroscopically and microscopically the surgical margins: transpancreatic, retroperitoneal and radial, created by the posterior wall of the surgical material. Assessment of the vascular and neural invasion is also recommended, as according to certain clinical studies it is associated with lymph nodes metastases and shorter life expectancy. Coagulative necrosis, local or geographic, is another prognostic factor, as it correlates with a high grade of histological malignancy of the tumour.

The morphological picture of the tumour, comprising tumour tissue architecture and characteristics of its cells, is also reflected in the tumour differentiation stage [51, 52]. Under a light microscope, PNEN usually corresponds to a well-differentiated neuroendocrine neoplasms G1 or well-differentiated neuroendocrine neoplasms G2. Organoid structures in the form of solid nests, trabecular or labyrinthine systems, or structures resembling glands and rosettes, are characteristic. They are accompanied by a varying quantity of tumour stroma and numerous blood vessels surrounding the tumour nests. It is worth emphasising that amyloid deposits are typical for a functioning tumour such as insulinoma, whereas glandular-like structures and psammomatous bodies are characteristic of somatostatinoma. The characteristics of neuroendocrine neoplasm cells are well known to differ from other neoplasms. They are small or medium-sized, with acidophilic or amphophilic and granular cytoplasm. The nuclei are round or oval, usually situated centrally in the cell. A typical feature of a NEN, which helps to distinguish it from adenocarcinoma, is fine-grained chromatin, referred to as 'salt and pepper'. Apart from the above typical features of neuroendocrine tumours, their cells may present a different picture, creating oncocytic, clear cell, fat-rich and rhabdo-like variants. PNENs may then resemble melanoma, clear cell renal cell carcinoma or adrenal cortical carcinomas. Diagnostic errors are caused by incorrect differentiation between a PNEN and a pancreatic ductal adenocarcinoma or acinocellular carcinoma, or clear cell carcinoma metastases from other organs.

To sum up, pathomorphological diagnostics of pancreatic NENs requires experience on the part of the pathomorphologist, co-operation of an interdisciplinary team of specialists, and access to an immunohistochemical laboratory.

Minimal consensus on pathology

Minimal histopathological report for a PNEN should include:

— *histological type of the neoplasm, considering the division into well-differentiated neuroendocrine neoplasms (NEN), neuroendocrine carcinomas (NEC) and mixed neoplasms (MANEC);*
— *histological G grading referring to well-differentiated neoplasms (NEN G1, NEN G2);*
— *pTNM staging according to ENET and AJCC/UICC classifications (it is important to provide affiliation of the classification in each case);*
— *assessment of surgical margins.*

*Histopathological diagnosis of NEN must be necessarily confirmed by immunohistochemical tests assessing expression of the neuroendocrine markers: synaptophysin and chromogranin A, as well as the Ki-67 proliferative activity using the MIB1 antigen [53] (*evidence level 3).*

2.3. Imaging diagnostics

2.3.1. Endoscopic diagnostics
Classical gastrointestinal endoscopy is practically of no importance for the diagnostics of PNENs.

2.3.2. Ultrasonography
Transabdominal ultrasonography
The sensitivity of conventional ultrasonography (USG), mostly performed as the first-line examination in the detection of primary tumours, and in assessment of the staging of the disease, is low for small tumours. On

* *evidence level according to CEBM [152]*

average, ultrasonography detects approximately 30% of primary insulinomas and gastrinomas. The sensitivity of this method increases for detection of hepatic metastases, when it amounts to 50–80%. For larger tumours, mostly non-secreting pancreatic tumours and late-diagnosed glucagonoma, the sensitivity of transabdominal USG is higher [54, 55, 56].

2.3.3. Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) enables precise imaging of the pancreas, and it is the most sensitive of the methods presently used in the diagnostics of pancreatic focal lesions (it detects lesions of 1–2 mm in diameter); normal results of EUS practically exclude the presence of a pancreatic tumour [57]. EUS imaging is useful when the CT scan image is inconclusive. Biopsy is recommended to confirm the neoplastic character of the lesion [58].

EUS enables the ability to:

— localise functioning neoplasms (diagnosed on the basis of clinical and/or biochemical symptoms);
— obtain the material for histopathological examination;
— tattoo small focal lesions before the planned surgical treatment;
— perform diagnostic imaging of non-functioning PNENs;
— conduct screening tests in patients with MEN1.

In the case of small insulin-secreting tumours, the EUS sensitivity is up to 94% [59–64]. Tumour location in the tail of the pancreas or the presence of small, slightly hypoechogenic nodules located deep into the pancreatic parenchyma and multifocal nodules can be a limitation for EUS [59, 65]. According to the literature, in the case of tumours in the pancreatic tail, the sensitivity of the examination can decrease to 60%. Diagnostic sensitivity of the examination in pancreatic gastrinoma tumours is nearly 100%, but it decreases in the case of multifocal lesions and those with an extra-pancreatic location; in the case of gastrin tumours located in the duodenum and outside the pancreatic parenchyma, the sensitivity of the test is estimated to be approximately 50% [63, 66].

EUS is also important in the differential diagnostics of PNENs of ambiguous character, and in pre-operative assessment of the neoplasm stage. There are certain specific ultrasonographic characteristics which allow differentiation between pancreatic carcinomas and neoplasms of the neuroendocrine origin, as well as between functioning and non-functioning neoplasms [67]. The usefulness of EUS for the assessment of the stage of lesions has also been confirmed, particularly for the evaluation of vascular invasion [68].

EUS is also used to perform fine-needle biopsy through the stomach wall. It is believed that this route of access, compared to percutaneous biopsy, reduces the danger of the spreading of neoplastic cells. In the study by Voss et al. [69], the diagnostic accuracy of such biopsy for pancreatic carcinoma was 81%, and for PNEN was 46.7%.

Presently, third generation contrast agents are entering ultrasound imaging. These agents are composed of gas microbubbles in a phospholipid shell, characterised by a long half-life in the bloodstream and enhanced, perfusion-dependent greyscale. Currently, studies are conducted on the use of contrast enhanced ultrasound (CEUS) for the differential diagnostics of pancreatic tumours, including PNENs [70]. CEUS detects tumours smaller than 2 cm in diameter with a sensitivity comparable to EUS (95%). With respect to PNENs, the method's sensitivity is up to 94%, specificity reaches 96%, the positive predictive value — 75%, and the negative predictive value is up to 99%. The image of neuroendocrine neoplasms has a characteristic echo pattern after intravenous administration of the contrast agent: in the arterial phase, echogenicity increases intensively and quickly decreases as the contrast agent washes out in the venous phase [2]. The highest accuracy in the differential diagnosis of pancreatic neoplasms and in detection of small (less than 1 cm) lesions is achieved by combining the EUS technique with intravenous administration of the contrast agent (*Contrast-Enhanced Harmonic Endoscopic Ultrasonography*, CH-EUS) [71].

In pre-operative diagnostics, it is possible to inject ink into the tumour tissue during EUS, which enables faster intraoperative location of the lesion. Using this method is important, especially in the case of laparoscopic procedures, during which it is impossible to palpate the pancreatic lesions. Apart from that, precise location of the lesion enables the ability to achieve an adequate resection margin and to preserve healthy pancreatic tissue. However, it is worth emphasising that tattooing may cause acute pancreatitis [72, 73].

A special indication for conducting EUS examination is MEN1. The incidence of pancreatic lesions in this group of patients is estimated as 40–80%. Although functioning neoplasms can be early diagnosed due to typical clinical and biochemical symptoms, non-functioning neoplasms (ca. 50% of lesions) in most patients are diagnosed late, which determines a poor prognosis. EUS is recommended as the most sensitive and economically justified method of monitoring these patients, as early detection of a pancreatic lesion enables the implementation of radical treatment.

2.3.4. Intraductal ultrasonography

Intraductal ultrasonography (IDUS) may surpass EUS in the detection of PNENs. In this method, a probe of

2 cm in diameter is introduced into the duct of Wirsung through the duodenoscope channel.

2.3.5. Intraoperative ultrasonography

The sensitivity of intraoperative ultrasound (IOUS) in the detection of small PNENs is similar to that of EUS. The sensitivity of this examination, combined with intraoperative palpation assessment, is up to 97%. In the case of gastrinoma, the sensitivity of the test within the pancreas is close to 100%, but decreases to 58% with extra-pancreatic location. IOUS also allows detection of multifocal tumours and metastases in the liver. IOUS examination is also performed during laparoscopy [74].

2.3.6. Computed tomography (CT) and magnetic resonance imaging (MR)

Presently, according to current guidelines, a spiral multidetector CT (MDCT) and MR imaging are used for the diagnosis of parenchymal abdominal organs. These methods are especially important in the assessment of the stage of the neoplastic disease, and in monitoring of the response to treatment [75]. They are also useful for the assessment of anatomical location and resectability of the primary lesion. Computed tomography enables performing a targeted biopsy from the lesion. The sensitivity of each imaging method depends on the location and type of tumour [64, 76].

Prior to administration of the contrast agent, functioning PNENs are usually isodense, rarely hypodense compared to the remaining pancreatic parenchyma, and calcifications are clearly visible. Most tumours are richly vascularised (insulinoma 80%), so in the arterial phase, MDCT is intensively enhanced. Metastases demonstrate a similar behaviour. Therefore, the MDCT examination should cover both pancreas and liver in the arterial phase. In this phase of the test, it is also possible to assess the tumour/coeliac arteries relation. In the parenchymal phase, the assessment is limited to the pancreas, and it concerns tumour morphology and the level of contrast washing out. The portal venous phase again comprises the pancreas, liver and hepatic portal system [77].

Some researchers have suggested conducting the examination also in the delayed phase (150 seconds after the administration of the contrast agent), and in order to further assess the level of washing out of the contrast material from the tumour. In typical neuroendocrine neoplasm, the contrast enhancement should decrease in the delayed phase relative to the arterial phase by at least 60 HU. Other types of enhancement in PNEN include uneven washout of the contrast agent (from more than half or from less than half of the tumour mass), or slowly increasing enhancement when the tumour is better visible in the equilibrium phase, in which the uptake in the normal pancreatic parenchyma decreases. This is a behaviour characteristic for tumours with a high connective tissue content. In the parenchymal and secretive phase, neuroendocrine neoplasms are not always isodense and are therefore invisible in the CT scan. Certain neoplasms in these phases of examination maintain the enhancement or only begin the process of collecting the contrast agent. Slightly enhanced neoplasms are usually poorly differentiated, so the level of enhancement correlates with the length of patient survival [78, 79]. Non-functioning neoplasm demonstrate a lower enhancement after the administration of the contrast agent, and are heterogeneous due to the necrotic areas. Calcifications in adenocarcinomas are very rare, whereas in functioning and non-functioning PNENs they are found in at least 25% of cases. In larger tumours, the pancreatic duct is dilated, and parenchymal atrophy is observed. The only features that distinguish malignant lesions from benign ones are invasion of the adjacent structures and distant metastases. Hepatic metastases are detected in the arterial phase of the examination [76].

Due to shortened time of scanning, a reduced number of movement artifacts, and obtaining thin (1–2 mm) tissue layers, MDCT enables multi-dimensional and spatial reconstructions, which facilitates imaging of structures smaller than 1 cm, and allows a complete assessment of the vascular invasion of the tumour [80]. The sensitivity of contrast-enhanced MDCT using 1 mm layers in diagnosis of insulinoma reaches 85–94% [81, 82], whereas for various types of NENs the sensitivity of multidetector CT is 50–90%, and the specificity is 96% [2, 83, 84].

The role of CT scans in the assessment of PNEN consists in the description of tumour morphology with precise location, and, with reference to organ-transgressing infiltration, in determination of the adjacent fat tissue invasion, infiltration of the duodenum, common bile duct, stomach, spleen, intestinal loops, adrenal glands, as well as determination of arterial and venous invasion, providing information about the invaded part and length of the vessel. The description should also contain information concerning enlarged regional lymph nodes and the assessment of the liver for metastases. Assessment according to TNM classification should be possible on the basis of CT description [1].

MR conducted according to the optimal protocol has a similar sensitivity in the diagnosis of PNEN as CT, which is up to 80–90%. MR offers a higher tissue resolution in combination with multi-dimensional imaging. Limitations of this method include: reduced availability (compared to CT scanning), higher price, longer duration of examination and the necessity of co-operation with the patient. The method is recommended espe-

cially for younger patients, as it does not require the use of ionising radiation, and also in patients whose CT scan image is inconclusive. Neuroendocrine neoplasms are hypointense on T1-weighted images, and hyperintese on T2-weighted images. Intravenous administration of the contrast agent increases sensitivity of the method [77]. In a multi-phase examination following the intravenous administration of the contrast agent, the images are enhanced according to the CT enhancement pattern provided above. In addition, in MR spectroscopy, which uses the chemical shift displacement, it is possible to determine the chemical composition of tissues. A relatively increased lipid content in NENs facilitates differentiation in uncertain cases.

In recent years, a diffusion weighted imaging (DWI) method has also been used, in which the level of water diffusion limitation in the tissue is assessed. Neuroendocrine neoplasms, particularly those with a high connective tissue content, cause limitation of the diffusion of water molecules, which generates an intensive signal in the DWI sequence, accompanied by lowered ADC. DWI is particularly valuable in tumours with a significant connective tissue component, which are poorly or atypically enhanced after intravenous administration of the contrast agent [54, 85].

2.4. Radioisotope diagnostics

The recently observed development of diagnostic methods with the use of labelled somatostatin analogues in examinations using the technique of single proton emission computed tomography (SPECT/CT) and positron emission tomography (PET/CT), also in combination with intraoperative detection with the use of isotope probe, contributes to higher detection rates of PNENs and their metastases. These tests can identify lesions undetected by anatomical imaging methods, increasing the chances of locating the primary focus and determining the actual stage of the neoplasm [76, 86]. They may also be the first-line method in the diagnostics of early recurrence, in monitoring the disease and in choosing the optimal treatment. A positive result of receptor scintigraphy is also the basis for introducing therapy with 'cold' and/or 'hot' (bound to a radioactive isotope) somatostatin analogues (SSA) [87, 88].

^{111}In-Octreoscan, used until recently in scintigraphic diagnostics, has been substituted in Poland with ^{99}Tc-EDDA/HYNIC-Tyr(3)-octreotide. The sensitivity of somatostatin receptor scintigraphy (SRS) for tests with the use of ^{111}In-Octreoscan in the diagnosis of the primary lesion for various PNENs has been estimated at 70–100% for gastrinoma, VIPoma and glucagonoma [89], at 50–60% for insulinoma [86], and at ca. 90% for non-functioning tumours. Scintigraphy with the use of ^{111}In-Octreoscan enables the ability to detect approximately 90% of GEP NENs hepatic metastases [90]. Generally, the sensitivity of SRS is estimated to be 71–96% [91], whereas the specificity ranges between 76% and 95% [89, 91]. Using the SPECT technique significantly improves the sensitivity of the method [89]. The usefulness of increasingly popular somatostatin analogues labelled with technet 99m for the diagnostics of PNENs has been confirmed by many authors [87, 92]. 99mTc-EDDA/HYNIC-Tyr(3)-octreotide (99mTc-EDDA/HYNIC-TOC) 99mTc-[99mTc-EDDA/HYNIC]octreotate demonstrates a higher uptake by the pancreatic and pituitary tumour cells having somatostatin receptors than octreotide. The possibility of combining scintigraphic and tomographic images with the use of fusion image SPECT/CT enables a precise detection of the anatomical location of the lesion visible in molecular imaging, and contributes to increased diagnostic sensitivity and specificity [93].

Presently, the most sensitive examination in the diagnostics of well-differentiated NENs is definitely the PET/CT test with the use of somatostatin analogues (SSA) labelled with ^{68}Ga: DOTA-TOC, DOTA-TATE and DOTA-NOC, and in the future probably also with ^{64}Cu-TETA-octreotide [94]. In the diagnostics of PNENs, it is also possible to use the PET/CT test with the use of ^{18}F-FDOPA. The usefulness of ^{18}F-FDOPA has been evaluated in different types of NENs and at different stages of the neoplastic process. Becherer et al. demonstrated a higher diagnostic sensitivity of ^{18}F-FDOPA PET compared to SRS and CT scanning in patients with advanced NENs, both with regard to staging and in the diagnostics of osseous metastases. However, SRS proved superior in planning treatment with SSA [95]. The examination with ^{18}F-FDOPA enables the exclusion of artifacts related to physiological activity in the peripancreatic tissues [44]. Other studies comparing ^{68}Ga with ^{18}F-FDOPA have indicated the indisputable superiority of the ^{68}Ga-DOTA-TATE test in the detection and staging assessment of NENs, whereas PET/CT examination with ^{18}F-FDOPA should be performed when the test with gallium is negative [96]. In the case of insulinoma, the diagnostic value of ^{18}F-FDOPA is disputable [97]. Another tracer used in diagnostics of PNENs is ^{11}C-5-hydroxytryptophan (5-HTP) [2]. It is not used in Poland. ^{18}F-Fluorodeoxyglucose (FDG) is used in the diagnostics of fast-growing and aggressive PNENs and PNECs with a poor prognosis.

The next step to improve sensitivity of location diagnostics of small PNETs (gastrinoma, insulinoma) is using an intraoperative radioisotope probe (RGS) [98, 99].

In recent years, new diagnostic tracers for PNENs have been introduced. They enable the location of certain types of functioning tumours, and due to diagnostic effectiveness in the future they may become

important imaging tools for PNENs. One of them is a labelled analogue of glucagon-like peptide-1 (GLP-1). Due to a very high expression of receptors for GLP-1 in some neoplasms (in 100% of benign insulin-secreting tumours), scintigraphy with the use of labelled GLP-1 analogues may become a diagnostic method competing with SRS [100]. Several reports concerning imaging of insulinoma on animal models and in humans have been published. A high tracer uptake by this tumour was demonstrated (high tumour/background ratio), and the quality of the received image was assessed as very good. Using a GLP-1 analogue labelled with ^{111}In, insulinoma implanted in a mouse was completely destroyed. In the study, the GLP-1 analogues labelled with ^{111}In (e.g. [Lys40(Ahx-DOTA-111In)NH2]-Exendin-4), 99mTc ([Lys40(Ahx-HYNIC-99mTc/EDDA)NH2]-exendin-4) and 68Ga were used. Preliminary study results indicate a lack of receptor expression for GLP-1 in most malignant forms of insulinoma (positive SRS is more common in these cases), which suggests the usefulness of imaging with labelled GLP-1 analogues for the differentiation of benign and malignant insulin-secreting tumour forms [101, 102].

2.5. Location diagnostics of different PNENs

2.5.1. Insulinoma

Most frequently they are small tumours, less than 2 cm in diameter (60–70% of cases), usually classified as group 1 according to the WHO classification; they are mostly single (85%) and located in 99% of cases in the pancreas, with a similar prevalence for all parts of the organ [10]. While conducting location diagnostics in the search for the cause of hypoglycaemia with hyperinsulinism, it should be noted that in approximately 4% of cases, the reason is hyperplasia of β cells (nesidioblastosis; NIPHS, noninsulinoma pancreatogenous hypoglycaemia). In the case of insulinoma, the most sensitive imaging examinations include endoscopic ultrasonography (EUS) and intraoperative USG. The usefulness of classical USG, EUS, IOUS, CT and MRI is discussed in detail in the section concerning the imaging diagnostics of PNENs.

Another test used in the diagnostics of insulinoma is SRS. It is important to note that only 50-60% of insulinoma tumours demonstrate somatostatin receptor expression (according to the literature data, the frequencies of expression for different SSTR types in insulinoma are as follows: SSTR1 — 51%, SSTR2 — 69%, SSTR3 — 62%, SSTR4 — 39%, and SSTR5 — 66%) [86]. If the results of other imaging tests are negative, a PET/CT scan with ^{68}Ga-somatostatin analogue may be performed [4]. Transhepatic portal venous insulin sampling (THPVS) and angiography with a selective calcium stimulation test [103] are very rarely used in diagnosing insulinoma. The methods are practically used only when other imaging techniques do not enable the locating of the focal lesion [10]. In the near future, GLP-1 analogue will probably play an important role in the diagnostics of hardly detectable, small insulinomas, due to GLP-1 receptor expression in all tumours of this type.

2.5.2. Gastrinoma

Gastrinoma is found mostly within the triangle: pancreatic head — duodenum — hepatic hilum. In 48–60% of cases, lymph nodes and hepatic metastases are present at the diagnosis, but in some groups of patients, the proportion of malignant neoplasms is up to 90% [104]. Multifocal lesions are also possible. The usefulness of USG, EUS, intraoperative USG, IOUS, CT and MRI examinations is presented in the section concerning the imaging diagnostics of PNENs.

Other examinations used for the diagnostics of gastrinoma include:

— somatostatin receptor scintigraphy (SRS). According to different authors, the sensitivity of gastrinoma detection ranges between 50% and 100% (according to the literature data, the frequencies of expression for different somatostatin receptors (SSTR) types are as follows: SSTR1 — 71%, SSTR2 — 50%, SSTR3 — 92%, SSTR4 — 78%, SSTR5 — 81%) [105]. SRS is the best examination to assess the early stages of the disease and the presence of distant metastases, but sensitivity of the test decreases to 50% if the tumour is smaller than 1 cm [4];
— intraoperative radioisotope probe. This method improves the sensitivity of detection of pancreatic primary lesions and metastases to the surrounding lymph nodes and to the liver;
— in the diagnostics of gastrinoma, scintigraphy with the GLP-1 analogue may also be used, due to the GLP-1 receptor expression in this tumour.

In the location diagnostics of small tumours, the combined use of a few diagnostic methods seems reasonable. In certain cases also performing angiography (the sensitivity of angiography is estimated at 30-50%) with venous catheterisation (AVSV) may be considered. In the case of gastrinoma located in the duodenum, intraoperative transluminescence is also used.

2.5.3. Location diagnostics of glucagonoma, VIPoma, somatostatinoma, non-functioning tumours and ACTHoma

At the moment of diagnosis, glucagonoma, somatostatinoma and NF-PNETs are usually large (approximately 5–6 cm), whereas VIPoma is slightly smaller (ca. 2 cm). The lesions are usually diagnosed late, and in approximately 70–90% of cases metastases are found already at

the diagnosis [16, 105]. Due to the size of lesions, they are easier to find by means of classical imaging methods (USG, CT, MRI). SRS, whose diagnostic sensitivity is 70–100%, is a standard examination in the assessment of the primary lesion, clinical staging (detection of metastases to the liver, lymph nodes, adrenal glands, spine), and in qualification for receptor radiotherapy [16, 86]. SSTR1 and SSTR2 expression is observed mostly in glucagonoma, SSTR5 in somatostatinoma, SSTR2 in VIPoma, and SSTR1, SSTR2, SSTR3 and SSTR5 in non-functioning neoplasms. Rare ACTHoma neoplasms also demonstrate somatostatin receptor expression. In the case of RF-PNENs, EUS is not recommended as the first-line procedure, but it may be used when MDCT, MRI and SRS-SPECT results are inconclusive. EUS may be useful in pre-operative diagnostics, whereas it is rarely necessary in patients with hepatic metastases [4].

2.5.4. Pancreatic endocrine carcinomas (PNECs)

In the location diagnostics of poorly differentiated PNECs and their metastases, all imaging examinations may be used: USG, CT, MRI, 18F-FDG PET, as well as SRS in tumours with overexpression of somatostatin receptors.

Summary of the diagnostics of PNENs

In the diagnostics of PNENs, both classical imaging techniques and nuclear medicine tools are used. The basic examination for patients with a PNEN is EUS, which enables location of the primary tumour site. Another examination is the SRS with ^{68}Ga or ^{99}Tc-DOTA TOC, which enables location of the primary lesion, but also assessment of the stage of the disease and qualification for treatment with 'hot' SSA. CT or MRI are next in the diagnostics of PNENs; their main role consists in the assessment of the stage of the disease. A PET/CT scan with ^{18}FDOPA may be an alternative diagnostic method if SRS results are negative. In the diagnostics of insulinoma, the role of a new isotope-labelled GLP-1 analogue is widely discussed.

Minimal consensus on imaging

The main examinations recommended in the diagnostics of PNENs include: EUS, CT, and MR, and next a radioisotope examination with a labelled somatostatin analogue (^{68}Ga or ^{99}Tc-DOTA TOC PET/CT,SPECT/CT) ***(*evidence level 3)****.*

3. Treatment of PNENs

3.1. Surgical treatment

Surgical treatment is the therapy of choice in the case of PNENs, as it is associated with significantly prolonged patient survival [2]. The development of diagnostic methods has improved the detection of small, asymptomatic tumours. Most non-functional neoplasms of ≤ 2 cm in diameter are benign and demonstrate a moderate risk of becoming malignant. Only 6% of non-functional, accidentally diagnosed PNENs present histopathological characteristics of malignancy [2]. In certain cases, tumours of ≤ 2 cm in diameter diagnosed accidentally may be observed for the first year, performing tests at three-month intervals, then every six months for the next three years [2]. Due to the lack of clear recommendations, the decision on the course of treatment should be taken by a multidisciplinary team of doctors experienced in the management of PNENs **(**evidence level 4*)**. When choosing surgical treatment, it is necessary to consider short-term and long-term effects of this therapy. According to the WHO classification, there is a correlation between the tumour size and its potential malignancy. Tumours of > 2 cm require an extensive surgery **(**evidence level 3*)** [44].

In multiple endocrine neoplasia type 1 (MEN1), if multiple lesions occur, it is recommended to remove them preventively before they become malignant; however, this approach in the case of small, non-functional neoplasms is still controversial **(**evidence level 3*)** [2]. In all cases, an intraoperative USG examination is recommended. The presence of multiple tumours sometimes requires a whole-organ resection. It is known that non-functional neoplasms associated with MEN1 should be removed if they are larger than 2 cm in diameter, fast-growing (annual growth of > 0.5 cm), and if metastases occur [2].

The type of surgical treatment of PNEN depends on its size, location, invasion of the adjacent organs, presence of distant metastases and the level of tumour malignancy, patient's general condition and the ability to control the clinical symptoms **(**evidence level 4*)**. Patients are qualified for a radical or palliative treatment, which only improves the quality of life **(**evidence level 4*)**. In the case of tumours located in the head of the pancreas, pancreatoduodenectomy is performed, whereas in tumours located in the body or tail of the pancreas, distal resection is conducted, with or without splenectomy **(**evidence level 4*)**. In certain cases of small and well-demarcated PNENs (non-functional neoplasms and insulinomas < 2 cm), atypical resections may be performed, including enucleation and resection of the middle segment **(**evidence level 3*)** [106]. Resection of the middle segment is performed only in the case of small lesions located in the pancreatic body. The condition of tumour enucleation is continuity of the duct of Wirsung [2].

** evidence level according to CEBM [152]*

Resection is necessary if the tumour is located < 3 mm from the pancreatic duct [4]. Enucleation of the lesion entails the risk of damaging or closing the duct of Wirsung, which is associated with complications [107]. These include acute postoperative pancreatitis and pancreatic fistula. Apart from the above complications, resection of a large part of the pancreas may cause the symptoms of exocrine and endocrine pancreatic insufficiency [108]. In certain cases, it is possible to conduct central pancreatectomy with a Roux-en-Y anastomosis of the pancreatic tail with a loop of the small intestine, and closing off the body of the pancreas.

Tumour resection should be considered even in the presence of metastases, including hepatic metastases, if they are potentially resectable, and the patient meets the criteria for the surgery **(**evidence level 4*)** [1, 44]. As PNENs are often malignant, it is necessary to remove the regional lymph nodes during resection **(**evidence level 3*)** [1, 108, 109]. In the case of enucleation and resection of the middle segment, it is also recommended to remove lymph nodes for histopathological examination [2, 107]. It is generally believed that PNECs should not be operated if disseminated metastases have been found in the diagnostic process **(**evidence level 3*)** [1].

Surgical treatment intended to remove the tumour (in the case of a resectable tumour) or reduce its mass (palliative therapy) in patients with disease limited to the primary tumour and regional lymph nodes should be standard procedure **(**evidence level 4*)** [44]. Resection should be performed only in those centres specialising in surgery of the pancreas. Laparoscopic resection of the pancreas is increasingly common, but the decision concerning whether to use an 'open' or a laparoscopic method should be taken by a pancreatic surgery specialist in the referential centre **(**evidence level 3*)**. Distal resections and laparoscopic enucleation of pancreatic tumours are presently considered to be safe [2]. In the case of a PNEN, an intraoperative USG examination is recommended.

The most common functional neoplasms are insulinoma and gastrinoma, while other tumours are rare RF-PNENs [4]. Gastrinoma is most often located in the head of the pancreas; in 60–90% it is a malignant neoplasm, and due to a frequent invasion of the lymph nodes, there are indications for regional lymphadenectomy [14]. It is recommended to remove the lesion radically to prevent hepatic metastases, which considerably worsen the prognosis. The scope of procedures depends on the tumour location and size, and comprises enucleations, resections of the middle segment, distal resections and pancreatoduodenectomies [109]. Laparoscopic procedures are not recommended [4]. In Zollinger-Ellison syndrome (ZES), which may be associated with MEN1 syndrome, surgical treatment is indicated if the tumour is larger than 2 cm. This approach is intended to prevent metastases [44] **(**evidence level 3*)**. Pancreatoduodenectomy is the recommended procedure (for tumours located in the head of the pancreas), as less extensive procedures are associated with recurrence in 90% of cases [4, 14].

Insulinomas are in 90% of cases benign; their removal does not require regional lymphadenectomy and where there is precise preoperative localisation of the tumour, laparoscopy is effective [110]. In the case of a suspected malignant insulinoma, or recurrence of the tumour, radical treatment is recommended, including excision of the recurrence and the possible hepatic metastases [4]. RF-PNEN include: VIPoma, glucagonoma, somatostatinoma, GRHoma and ACTHoma. In this group of tumours, radical surgical treatment is recommended even if hepatic metastases occur, and the scope of resection and lymphadenectomy corresponds to the procedures implemented in gastrinoma. Laparoscopic procedures are not recommended **(**evidence level 3*)** [1, 4].

In advanced F-PNENs, resection is intended to reduce the symptoms and the tumour mass. Cytoreduction may be considered if removal of 90% of the tumour mass is possible, even if hepatic metastases are present. Removal of 90% of the visible tumour mass is possible in only 5–15% of cases [14, 111]. R1 resections of PNENs are not associated with a worse survival rate than R0 resection [107]. Cytoreduction may be performed with radiofrequency thermoablation (RFA) **(**evidence level 3*)**, which can also be conducted laparoscopically. This method may be used if there are fewer than ten focal lesions in the liver, and if the largest one is < 5 cm in diameter (optimally 3 cm). This method enables the control of symptoms in over 90% of patients [112].

Radical excision of hepatic metastases is the 'gold standard' in the therapy of advanced PNENs, therefore resection should be performed whenever it is possible **(**evidence level 4*)**. The method of resection depends on the patient's general condition, and the size, location and number of metastases. It comprises enucleation, wedge excision of a fragment of the liver, excision of a segment/segments, non-anatomical resection or hemihepatectomy. Resection of hepatic metastases of PNENs is considered only in cases of G1 and G2 neoplasms [113]. It depends on the resectability of the lymph nodes, lack of micronodular or non-resectable dissemination in the peritoneum, or distant metastases outside

** evidence level according to CEBM [152]*

of the abdominal cavity [113]. R2 resection should be considered in selected cases of functional neoplasms which do not respond to conservative treatment, in order to reduce the intensity of the symptoms **(**evidence level 3*)**. Excision of the primary tumour, lymph nodes and hepatic metastases, combined with thermoablation, may reduce the tumour mass by more than 90% [113]. In the case of unresectable metastatic lesions in the liver, cholecystectomy should be performed during surgery to prevent ischaemic complications of the gall bladder resulting from a possible implementation of (chemo) embolisation. Resection of hepatic lesions may be performed in one or two stages, depending on the location and size of the metastases [107]. Other methods of treating metastases include locoregional therapies (variants of ablation, embolisation) and liver transplantation. It is assumed that transplantation is conducted in selected groups of patients with exacerbated symptoms associated with hormonal secretion. Patients who may benefit from transplantation are those under the age of 50, without metastases outside the liver, and with a low expression of Ki-67 and E-cadherin [109].

If resection of hepatic metastases is impossible (unresectable or inoperable lesions), the recommended treatment methods include hepatic artery embolisation (HAE), transarterial chemoembolisation (TACE) or embolisation with the use of isotope **(**evidence level 3*)**. Currently, these methods are considered to be safe [14]. RFA, cryoablation and microwave ablation (MWA) can be used for tumours ≤ 5 cm [111].

In the case of a diagnosis of peritoneal dissemination, surgical treatment is controversial and is recommended only in a selected group of patients. Even in some patients with unresectable liver disease, resection of the primary tumour together with macroscopic intraperitoneal nodules makes it possible to focus further therapies exclusively on the liver disease [114]. There is no consensus on the simultaneous resection of hepatic and intraperitoneal lesions. If an extensive surgery of the liver with resection of peritoneal lesions is necessary, dividing the procedure into stages, conducting the resection in a specialist centre, and introducing multidirectional treatment should be considered. Presently, the combination of surgery and perioperative intraperitoneal chemotherapy, as well as intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) are in the experimental phase [114].

If tumour resection and the elimination of symptoms are not possible, a palliative surgical management is implemented, which can significantly affect the quality of life. This is used after exhausting all non-surgical methods, mainly when the tumour is responsible for mechanical jaundice, chronic pain and gastrointestinal obstruction or bleeding. The treatment method is individualised for each patient. If mechanical jaundice occurs, it is recommended to perform anastomosis between the bile duct and intestine, or drainage of the bile tract. When an unresectable pancreatic tumour disturbs the passage of food through the duodenum, bypass surgery is recommended, usually a gastrointestinal anastomosis. The method of surgical management of chronic pain is coeliac plexus neurolysis and/or thoracoscopic section of the splanchnic nerve. Treatment of patients with PNEN should be comprehensive and conducted by a multidisciplinary team of doctors; the surgery should be performed in a centre specialising in pancreatic surgery **(**evidence level 3*)** [44].

Minimal consensus on surgical treatment

— *Accidentally detected non-functional neoplasms of ≤ 2 cm in diameter, without evidence of histopathological malignancy may be observed, and the decision on the course of treatment should be taken by a multidisciplinary team of doctors experienced in the management of PNENs. Tumours of > 2 cm require an extensive surgery with lymphadenectomy.*

— *In certain cases of small (< 2 cm) and well-demarcated PNENs (non-functioning neoplasms and insulinomas), atypical resections may be performed, including enucleation and resection of the middle segment (it is necessary to collect the lymph nodes for histopathological examination). Distal resections and enucleations may be performed laparoscopically.*

— *Tumour resection should be considered even in the presence of metastases, including hepatic metastases, if they are potentially resectable and the patient meets the criteria for the surgery. It is believed that PNECs should not be operated if disseminated metastases have been found in the diagnostic process.*

— *In advanced functioning PNENs, resection is intended to reduce the symptoms and the tumour mass. Cytoreduction may be considered when the removal of 90% of the tumour mass is possible, even if hepatic metastases are present (*evidence level 3).*

— *In cases of unresectable hepatic metastases, the recommended palliative treatments include HAE, TACE or embolisation with the use of a radioisotope. RFA, cryoablation and MWA can be used in tumours ≤ 5 cm (*evidence level 3).*

Liver transplantation is conducted in a selected groups of patients with exacerbated symptoms associated with hormonal secretion. Patients who may benefit from the transplant are

** evidence level according to CEBM [152]*

*those under the age of < 50 years, without metastases outside the liver, and with a low expression of Ki-67 and E-cadherin (*evidence level 3).*

3.2. Endoscopic treatment of PNENs

The treatment of PNENs is generally surgical, and endoscopic management is only symptomatic.

Endoscopy may be used in the symptomatic treatment of:

— mechanical jaundice (prosthesis of the biliary duct);
— obstruction of the gastrointestinal tract (prosthesis of the gastrointestinal tract lumen);
— control of gastrointestinal bleeding (the use of endoscopic hemostatic methods).
— EUS-controlled coeliac plexus neurolysis (CPN), described for the first time in 1996, involving administration of 0.25% bupivacaine solution, followed by 98% alcohol, is an alternative method for the management of chronic pain associated with pancreatic tumours [115].

In recent years, single cases of using EUS for ablation of F-PNETs secreting insulin have been reported [116–118]. It is possible that in the future endoscopic EUS-controlled ablation of PNETs, involving administration of cytotoxic agents, alcohol or using thermoablation will become a therapeutic method for patients who cannot be treated surgically **(*evidence level 4)**.

3.3. Medical treatment

The main purpose of pharmacological treatment is prevention of the symptoms of the disease and maintaining the patient's good quality of life (QoL) for the longest possible time [44]. Prior to planning the treatment, the tumour size, presence of metastases, histological grading and the profile of secreted peptides and markers should be determined **(*evidence level 4)**.

The choice of the treatment method depends on the symptoms, staging of the disease, the level of radiotracer uptake in receptor scintigraphy and histological characteristics of the tumour [119] **(*evidence level 4)**.

For non-surgical NENs, the goal of the treatment is alleviation of symptoms of the disease, maintaining optimal QoL and, if possible, prolonged survival **(*evidence level 5)**.

3.3.1. Symptomatic treatment

Symptomatic treatment should be started when the clinical and biochemical symptoms indicate hormonal activity of the NEN, even before the precise location of the primary site or confirmation of metastases. The symptoms associated with excessive secretion of hormones by PNENs may impair the patient's quality of life, and in certain cases they may be life-threatening (e.g. severe diarrhoea and hypokalaemia in VIPoma or carcinoid crisis).

Pharmacological treatment mostly involves somatostatin analogues and other medications, such as IPP in gastrinoma or diazoxide in the case of insulinoma. Additional symptomatic medications, such as loperamide, cholestyramine and corticosteroids are used if necessary. Bisphosphonates can be used for pain management in patients with osseous metastases.

Functioning pancreatic neuroendocrine neoplasms (F-PNENs)

Somatostatin analogues (SSA)

Using somatostatin analogues (octreotide, lanreotide) is the 'gold standard' therapy of functioning PNENs, regardless of the tumour size [1, 120]. The recently published CLARINET study, involving 204 patients with GEP NENs (45% of patients with PNENs), also proved the antiproliferative effect of Lanreotide Autogel in a randomised, placebo-controlled phase III trial [121] **(*evidence level 1)**.

New somatostatin analogues

SOM-230 (pasireotide) is a new analogue of somatostatin (SSA). In phase II studies, pasireotide was used for symptomatic treatment in patients resistant to conventional therapy (octreotide and lanreotide).

Interferon α

Interferon α is used in the treatment of both functioning and non-functioning NENs, in monotherapy or combined with long-acting SSA, if the patient does not respond to the treatment with maximum SSA doses. Interferon α may also be used in symptomatic treatment, but it is usually introduced as a second-line treatment due to its unfavourable toxicity profile [1]. Sometimes it is used as an adjuvant therapy in patients with clinical syndromes which cannot be controlled with SSA.

Insulinoma

Pharmacological treatment of insulinoma is intended to prepare patients for a surgical procedure, or to achieve biochemical control in patients with inoperable metastatic insulinoma. Apart from frequent meals of small volume, patients require intravenous glucose administration. Despite this treatment, hypoglycaemia often requires additional medications to control the serum glucose concentration. In most patients with insulinoma, diaxozide has proved to be effective in controlling the symptoms of hypoglycaemia [4]. *Diazoxide* is used for short-term treatment of patients with insulinoma awaiting surgery, or for long-term treatment of patients with inoperable tumours. Diazoxide is an antihypertensive medication with an additional hyperglycaemic

** evidence level according to CEBM [152]*

effect, as it inhibits insulin secretion by a direct action on pancreatic β cells and activation of glycogenolysis. The recommended daily dose is 50–300 mg orally, up to 600 mg/d. This is usually an effective treatment in controlling the symptoms of hypoglycaemia in patients with insulinoma. Adverse events, including oedema, increased body weight, hirsutism and renal function disorders are common, but usually tolerable.

Diazoxide therapy is often supported with hydrochlorothiazide at a dose of 25 mg/day, which prevents oedema, hyperkalaemia and increases the hyperglycaemic effect of diazoxide.

Verapamil and ***diphenylhydantoin*** (phenytoin) can be used to control glycaemia, as an alternative to diazoxide, in some patients with insulinoma. ***Corticosteroids***, including prednisolone, are usually used in insulinoma patients resistant to the treatment of hypoglycaemia.

SSA (octreotide and lanreotide) are used in patients with confirmed somatostatin receptor type 2 expression on the tumour cells [119]. They are often ineffective in controlling hypoglycaemia (50–60% of insulinomas) and their effect on the blood glucose concentration varies [122]. In some cases, they may even intensify hypoglycaemia by inhibiting glucagon secretion [4, 123].

In some patients, using interferon α may be beneficial in treating hypoglycaemia [34]. An mTOR inhibitor — ***everolimus*** — is one of the medicines controlling insulin secretion and hypoglycaemia in patients with malignant insulinoma [4].

Gastrinoma

Pharmacological treatment of gastrinoma is discussed in the section on gastroduodenal NENs (*pp. 444–458*).

VIPoma (symptoms: watery diarrhoea, hypokalaemia, achlorhydria (WDHA), Verner-Morrison syndrome)

Hydration and supplementation of electrolytes is recommended, as they may considerably improve the patient's clinical condition. In patients with VIPoma, accompanied by a rare life-threatening syndrome, administration of SSA significantly relieves the symptoms (in 80–90% of patients) and lowers the concentration of vasoactive intestinal peptide (60–80%) [124]. Biochemical improvement does not always correlate with clinical improvement, so a dose titration based on patient's clinical condition is necessary. Corticosteroids are used in patients with life-threatening diarrhoea which does not respond to the maximum doses of SSA.

Glucagonoma

Following introduction of SSA treatment, 80–90% of patients with glucagonoma demonstrate a visible clinical improvement (reduced skin lesions due to necrolytic erythema), although the treatment is less effective in controlling diabetes and weight loss. SSA reduces blood glucagon concentration in approximately 60% of patients, although normalisation of this parameter is unlikely [125].

Zinc salts may be used in patients with glucagonoma to prevent further skin damage. ***Antithrombotic prophylaxis*** should be considered in all patients with NEN associated with an increased risk of thromboembolic complications (e.g. glucagonoma).

Long-acting SSA are also effective in fighting the symptoms of ectopic hypersecretion in some cases of somatostatinoma [4]. They may also be useful in patients with paraneoplastic syndromes, e.g. Cushing's syndrome and acromegaly, associated with ectopic secretion of ACTH or the growth-hormone-releasing hormone (GHRH).

In recent years, there has been growing interest in the use of glucocorticosteroid receptor antagonists, e.g. mifepristone, as well as dopamine agonists, e.g. cabergoline, in the treatment of Cushing's syndrome.

SSA have been proven effective in controlling hypercalcaemia associated with the hypersecretion of the parathyroid hormone-related peptide (PTHrP) in rare PNENs secreting PTHrH [126].

Non-functioning pancreatic neuroendocrine neoplasms (NF-PNENs)

Somatostatin analogues demonstrate antiproliferative effects, confirmed in patients with NENs. PROMID was the first phase III study, which revealed such effects of octreotide in the midgut tumours, both functioning and non-functioning ones [127]. In patients with PNENs, observational studies have demonstrated partial or complete response in less than 10% of patients, and radiological stabilisation of the neoplasm in 24–57% of patients [128–130]. The results of the CLARINET phase III study have confirmed the antiproliferative effect of Lanreotide Autogel in patients with non-functioning PNETs with low proliferation index (Ki-67 < 10%) [121, 131].

3.3.2. Chemotherapy and targeted treatment

Chemotherapy is discussed in detail in section I of "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumors)" (*pp. 418–443*)

Given the present state of knowledge, there is no evidence that any adjuvant therapy (i.e. additional therapy after radical surgery) has a positive effect on extend-

** evidence level according to CEBM [152]*

ing disease-free survival (DFS) and/or overall survival (OS) of patients with PNENs. This applies primarily to G1/G2 NENs [132]. In the case of neuroendocrine carcinoma (NEC), an adjuvant therapy based on platinum analogues should be considered. Although there are no phase III randomised prospective studies, it seems that chemotherapy including cisplatin (or carboplatin) with etoposide may prolong disease-free survival in patients with NECs **(**evidence level 4*)**. The use of adjuvant radiotherapy or radiochemotherapy is not scientifically supported.

In patients with advanced NECs, the basic therapy is chemotherapy including platinum analogues plus etoposide [132] **(**evidence level 3*)**.

The best results in the chemotherapy of advanced NENs have been achieved in G1/G2 NETs of pancreatic origin. The use of streptozotocin (STZ) in monotherapy resulted in a response rate (RR) of approximately 36%, and OS of ca. 17 months. Combining streptozotocin with 5-fluorouracil (5-FU) increased the response rate to 63% and extended the mean overall survival to 26 months [133]. A breakthrough in chemotherapy of G1/G2 NENs was the phase III study by Moertel et al. in 1992 [134], in which 69 patients were randomised to two chemotherapy arms: streptozotocin-based, i.e. with doxorubicin (DOX) *v.* chemotherapy with 5-FU, demonstrating RR of 69% *v.* 45%, respectively, with the mean clinical response time of 18 months *v.* 14 months, and the mean overall survival of 26 months *v.* 17 months (****evidence level 3***).

The effectiveness of the chemotherapy of well/medium-differentiated GEP NENs should be considered separately for neoplasms of pancreatic origin and those with different locations (stomach, duodenum, small intestine, appendix and colon). Indirect comparisons of the results of clinical studies involving patients with GEP NENs have demonstrated a higher probability of response in patients treated due to PNENs (15–35% compared to 5–15%) [135].

In well-differentiated PNENs, the highest activity in monotherapy (response rate: 20–40%) is demonstrated by streptozotocin, doxorubicin, fluorouracil, dacarbazine and temozolomide. Multi-drug regimens are more effective then monotherapy regarding the effect on the response and survival rates (mean survival — 15–30 months).

The expert panel recommends combining streptozotocin (the medicine is not registered in Poland, available as direct import) with doxorubicin and 5-fluorouracil, and using a two-drug chemotherapy in patients with a greater risk of complications or not qualifying for the treatment with anthracyclines.

3.2.3. New targeted therapies [44]

In patients diagnosed with advanced PNENs (locally advanced stage, without a possibility of surgical treatment and disseminated stage), it is now possible to use molecularly targeted drugs (sunitinib and everolimus) in the case of progression of the disease (progression within the last 12 months assessed on the basis of imaging examinations results and the RECIST classification). Sunitinib is indicated in the case of well-differentiated neoplasms (NENG1), and indications for everolimus comprise well- and moderately-differentiated neoplasms (NENG1 and NENG2) [136, 137]. These medications — everolimus (a serine/threonine kinase — mTOR — inhibitor) and sunitinib (a tyrosine-kinase inhibitor) [138] significantly extend progression-free survival (PFS) by approximately 5.5–6 months. Adding everolimus to octreotide (the RADIANT-3 trial) extended progression-free survival by approximately five months (16.4 *v.* 11.3) compared to monotherapy with SST analogue.

In patients with malignant insulinomas resistant to conventional treatment, using everolimus significantly improved the control of glycaemia [139, 140].

Everolimus and sunitinib may, in justifiable cases, be used as the first-line treatment in patients with advanced well-differentiated PNENs (documented radiological progression within 12 months) **(**evidence level 1*)**.

Using sunitinib and everolimus is associated with a number of unresolved problems (e.g. the order of use for various treatment methods, selection of patients for specific medications, the ability to anticipate effectiveness, and adverse reactions). The value of sunitinib and everolimus in poorly differentiated PNECs, and the possibility of combining them with other methods (e.g. adjuvant postsurgical treatment) also require clarification.

The effectiveness of pazopanib (another multikinase inhibitor), demonstrated in the phase II studies, needs to be confirmed, which is particularly important due to a generally better tolerance of the treatment.

Minimal consensus on the medical treatment in pancreatic NENs

*Functioning G1/G2 PNENs — somatostatin analogues (*evidence level 1), and in the case of progression of the disease, adding everolimus (*evidence level 1).*

*Advanced non-functioning G1/G2 PNENs — systemic chemotherapy including streptozotocin with doxorubicin (± 5-FU) (*evidence level 3) and/or a somatostatin analogue (*evidence level 1). If the disease progresses after chemotherapy, everolimus or sunitinib (*evidence level 1). Targeted*

** evidence level according to CEBM [152]*

therapy can be considered as first-line therapy in selected cases as an alternative treatment to chemotherapy.

*The basic treatment of PNEC is chemotherapy based on the cisplatin plus etoposide regimen (*evidence level 3).*

3.4. Radioisotope treatment

Isotope therapy with labelled SSA (PRRT, peptide receptor radionuclide therapy) is now becoming a recognised form of palliative treatment, giving a chance for stabilisation or partial regression of the neoplastic disease, and less often for a complete remission [141, 142]. De Jong et al. [141] in 1998 published the results of a multicentre study involving a group of 256 patients with GEP NENs, including PNENs, treated with ^{90}Y DOTA TOC.

In 27% of the patients, a partial response to the treatment was observed, and in individual cases a total response was achieved. The results of the ^{90}Y/^{177}Lu DOTA TOC therapy in a group of 20 patients, including 15 with PNEN, were presented in 2006. Regarding the patients with PNEN, the authors observed stabilisation of the disease in eight patients, partial remission in four patients, and progression of the disease in three patients [143]. Presently, more common in PRRT is [Tyr3]octreotate (DOTA TATE), an analogue which demonstrates a higher affinity to SSTR2 than the previously used ones. The therapy has been successfully conducted in a few centres in Poland, also in patients with PNENs, after confirming a high somatostatin receptor expression in the primary/meta tumour in SPECT or PET examination. It is now believed that, similarly to GEP NEN of different locations, the therapy may be introduced without a prior chemotherapy. Based on the observations in patients treated with chemotherapy before the isotope treatment, is has been established that myelotoxicity and nephrotoxicity occur more often.

Similarly to other GEP NENs, the main indications for the treatment of PNEN with labelled SSA are advanced and inoperable NENG1 or NENG2. In individual cases, this therapy may be used in NEC with a sufficient somatostatin receptor expression, especially if the disease progresses and other treatment options have been exhausted [2, 4, 34]. Isotope therapy may be considered in the case of non-surgical recurrence and primarily, as a form of neoadjuvant treatment if surgical management is impossible due to a significant local advancement of the tumour [144]. Recent reports point to the possibility of using PRRT much earlier, before the surgery of unresectable lesions, mostly in the case of PNENs. The authors used both ^{90}Y and ^{177}Lu isotope combined with a SSA. Among the patients receiving PRRT as noeoadjuvant treatment of an inoperable primary tumour, there were single cases of patients with hepatic metastases, in whom the isotope therapy resulted not only in regression of the tumour mass, but also of the metastatic lesions [145, 146]. Due to a limited group of patients receiving this form of treatment, there is no strong evidence for introducing PRRT prior to a non-surgical procedure in the management guidelines; however, this form of treatment may be individually considered, depending on the patient's clinical condition, advancement of the disease and the proliferation index of the neoplasm. Each time while deciding on the isotope treatment, adverse reactions associated with this form of therapy should be taken into account. In the case of PNENs with insufficient SSTR2 expression, indications for the ^{90}Y and ^{177}Lu DOTA TATE therapy may be limited. In overexpression of SSTR5, another radiotracer, i.e. ^{90}Y DOTA LAN may be used [34]. Expression of this type of receptor may also be present in well-differentiated neoplasms, especially those which lost the active SSTR2 during therapy, as a result of treatment with SSA (tachyphylaxis) [34].

PRRT may also be used to treat functioning PNENs. In the case of malignant lesions, it is possible to conduct isotope treatment [10, 34] as a form of palliative management with temporary therapeutic response. In patients with diffuse gastrin tumour and positive receptor scintigraphy results, eligibility for PRRT should be considered. However, similarly to other PNENs, this therapy requires studies involving a larger number of patients in order to establish its actual therapeutic value [104]. Based on individual reports in the literature, it is known that gastrinomas respond to therapy faster, but early progression is relatively frequent [34].

The treatment with 'hot' SSA is a relatively new form of therapy, used mainly as palliative treatment, without any expectations regarding the impact on partial remission of the disease or the patient's survival. Some new publications have indicated a possibility of using PRRT as second-line therapy in the case of disease progression, following stabilisation or remission achieved with this method. It appears that re-implementation of isotope treatment at the maintained expression of somatostatin receptors may prolong the patient's survival without a significant exacerbation of adverse reactions associated with this therapy [147]. Radioisotope treatment is frequently combined with 'cold' SSA (including non-functioning neoplasms). Monitoring of the effects of PRRT comprises not only imaging examinations,

** evidence level according to CEBM [152]*

but also monitoring of CgA and the markers specific for functioning PNENs. In PNEN, CgA is a prognostic factor of PFS [148].

Among different forms of PRRT in NETs, including PNENs, radioembolisation with yttrium-labelled microspheres is used, in which the response rate is estimated at 52–66% and the mean survival is 70 months [149, 150]. According to Ramage et al. [151], a complete remission of the disease is achieved in 2.7% of patients, and a partial remission in 60%. Since there are no reports on the use of radioembolisation in a larger group of patients, further studies in this field are necessary.

Position of PRRT in the management of PNENs

In both functioning and non-functioning PNENs, the basic form of treatment is surgery. In the case of advanced disease and non-functioning neoplasms, the treatment with labelled somatostatin analogues may be considered as the first-line therapy of disease progression, preceding other forms of management. Chemotherapy may be introduced as the second-line treatment if the disease progresses, especially when SSTR expression is lost.

The next stage in the management of secreting tumours progressing after the surgical treatment is using 'cold' SSA. Isotope treatment should be considered as the second-line treatment.

Minimal consensus on PRRT

*PRRT may be used in advanced, inoperable PNENs, especially G2 and G1 (*evidence level 3). PRRT may be considered in individual cases with NEC, provided a high somatostatin receptor expression is confirmed and other forms of therapy prove ineffective (*evidence level 4).*

*In functioning neoplasms of the pancreas, PRRT as the second line treatment, after a 'cold' SSA (*evidence level 3).*

*In non-functioning tumours of the pancreas, PRRT may be considered as the first-line therapy, preceding other forms of palliative treatment (*evidence level 4).*

In both cases, surgical management is the basic form of treatment.

5. Follow-up

This is discussed in detail in section I of "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumors)" (*pp. 418–443*).

Minimal consensus on follow-up

Monitoring of the treatment should be individualised according to histological differentiation of the NEN (G1, G2 or G3) and the disease staging.

Follow-up comprises clinical examination, determination of the concentration of CgA and specific markers (in functioning neoplasms, depending on the clinical symptoms), as well as radiological (USG, CT/MRI), endoscopic and functioning (SRS) examinations. The frequency of examinations depends on the stage of the disease (2–3 months for NECs and 6–12 months for G1 and G2 PNETs).

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152. OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653 * OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson.

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